

Endpoints and Study Design Considerations for Therapeutic Cancer Vaccines

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“The findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.”



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Regulation of Cancer Therapeutics in the US

- Office of Oncology Drug Products, CDER
 - Drugs (small molecules)
 - Biologics, including
 - Monoclonal Antibodies
 - Therapeutic Proteins
 - Cytokines
- Office of Cellular, Tissue and Gene Therapy, CBER
 - Cell therapies
 - Gene Therapies
 - Cancer vaccines

CDER OCTGT Regulated Products

- Cellular therapies
- Cancer vaccines
- Other cancer immunotherapies
- Gene therapies
- Tissue and tissue based products
- Combination products
 - Biologics/Drugs
 - Biologics/Devices

CDER Office of Cellular, Tissue, and Gene Therapies

Celia M. Witten, Ph.D., M.D., Director
Stephanie Simek, Ph.D. Deputy Director

Division of Cellular and Gene Therapies

Raj Puri, M.D., Ph.D., Director
Kimberly Benton, Ph.D., Deputy Director

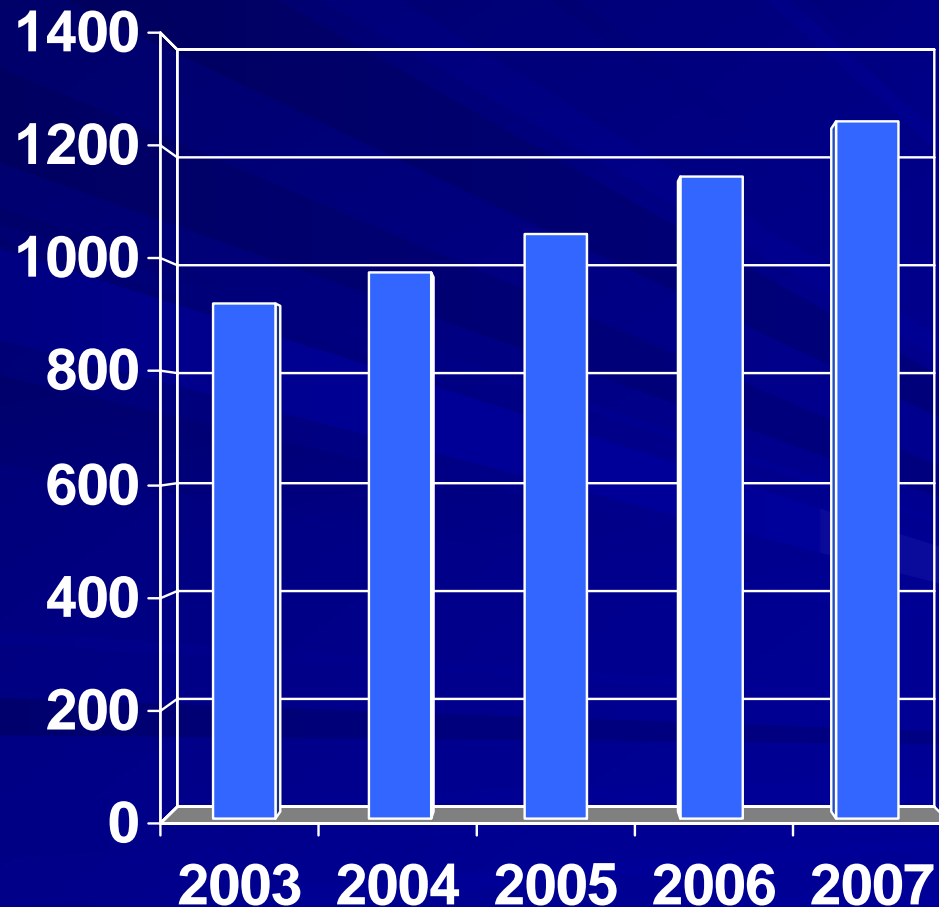
Division of Human Tissues

Ruth Solomon, M.D., Director

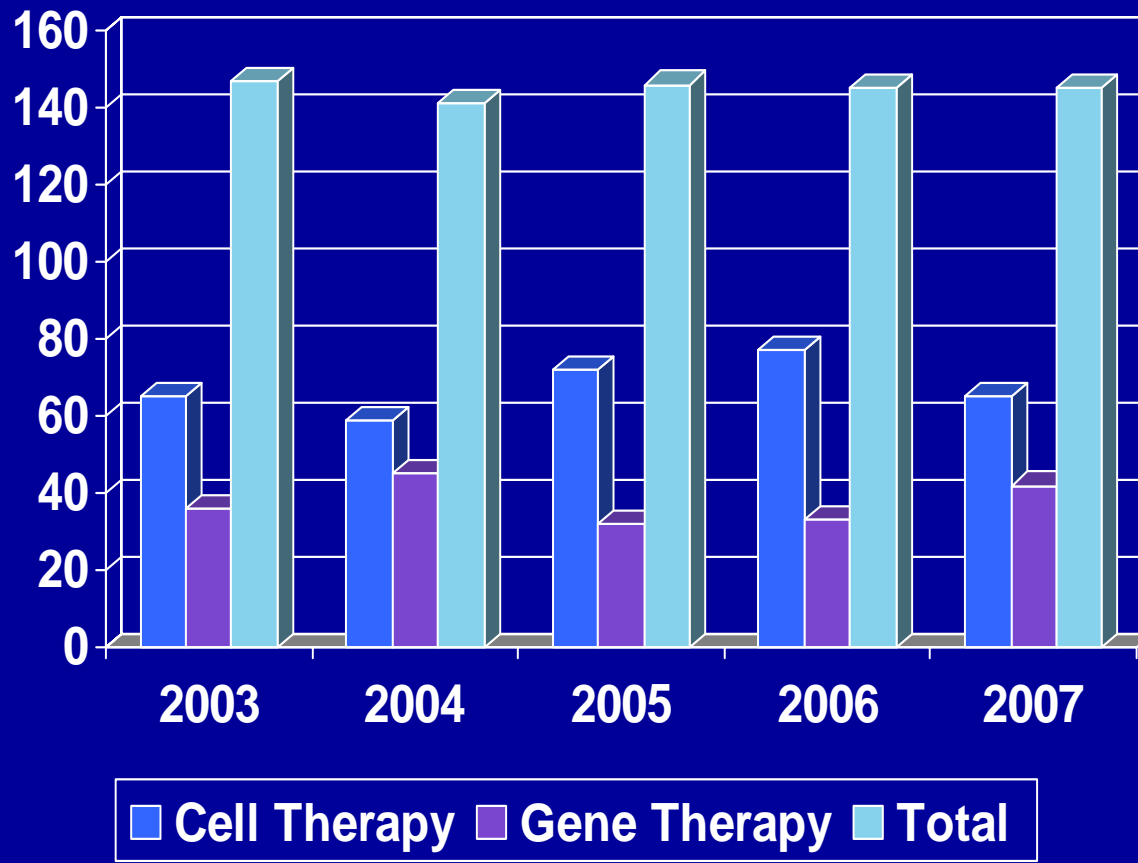
Division of Clinical Evaluation and Pharmacology/Toxicology

Ashok Batra, M.D., F.A.C.S., Director

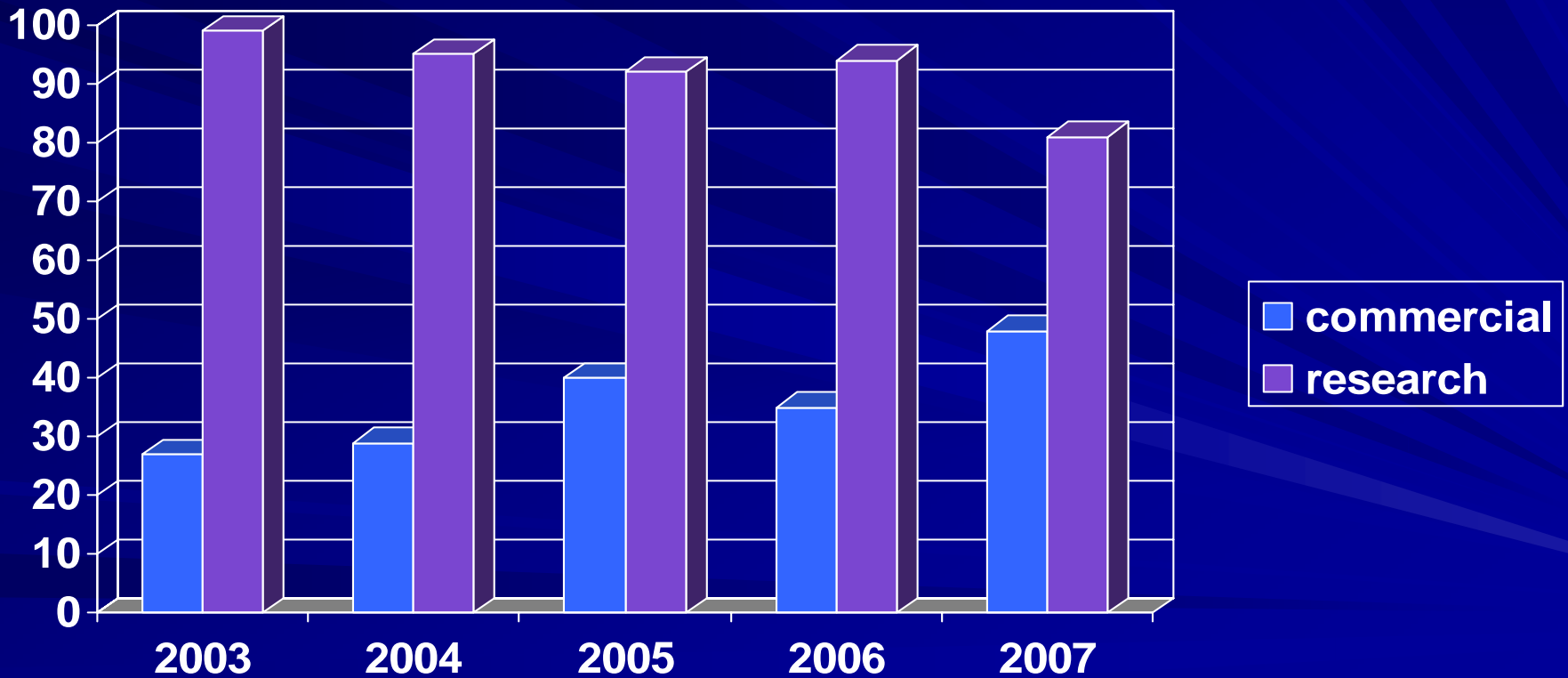
Active Files in OCTGT (IND, IDE, MF) FY 2003-2007



New Applications FY 2003-2007



New Application Sponsors Commercial vs. Research



Cancer Vaccine Clinical Development Considerations

■ Early Phase goals

- Choose starting dose and regimen
 - Based on preclinical information and FDA advice
- Describe preliminary safety profile
- Dose escalation schemes
 - 3 + 3 design may not be most appropriate design
 - MTD may not be identified, but we need DLT defined
 - Optimal biological dose is a rational goal
 - Consider immune response monitoring
- Proof of concept

Cancer Vaccine Clinical Development Considerations

- Is there a biomarker involved?
 - Suggestive of activity (PSA, CA-125, etc.)
 - Support proof of concept
 - Help optimize regimen
- Consider Assay-therapeutic co development issues if a specific antigen or target is required for eligibility
 - Anticipate assay development requirements
 - May need CDRH input, IDE
- Consider Immunological monitoring
 - May help optimize dose
 - Achieve a better understanding of immunological mechanisms
 - T cell responses
 - T Regulatory cells effects
 - Th1/Th2 cells

Cancer Vaccine Clinical Development Considerations

- When choosing a therapeutic indication consider
 - Target Ag expression in nl and tumor tissue
 - Availability of tumor tissue samples for
 - Screening patients for target antigen
 - Studying in vivo effects
 - Stage of disease
 - Advanced disease may reach endpoint sooner
 - Earlier disease may be more immune competent
 - Vaccine may potentiate subsequent therapy
 - Available therapy for proposed indication

Cancer Vaccines: Completed Phase 3 clinical trials

- Renal Cancer (N=1460)
- Breast Cancer (N=1028)
- Pancreatic Cancer (N= 255)
- Follicular NHL (N=636)
- Melanoma, Allogeneic (N=3074)
- Melanoma, Autologous (N=818)
- Prostate (N=1034)

Phase 3 clinical trials with Cancer Vaccines

- Therapeutic Cancer vaccines have not yet demonstrated clinical benefit in phase 3
 - 8000+ patients randomized
 - Multiple indications, product types:
 - Cell therapy vs. gene therapy
- No successful paradigm thus far
- OCTGT encourages discussions following phase 3 regardless of outcome
 - “Lessons learned”

“Lessons learned” from sponsors

- Determine need for adjuvant early in preclinical development.
- Develop potency assay early in development
- Always do at least one randomized phase 2b study and preferably two
 - Preliminary estimate of treatment effect
 - Confirm proof of concept
 - Refine population for phase 3
 - Understand kinetics of immune response
- Choice of control may affect results
 - KLH, BCG may have clinical activity

Planning Later Phase Studies

- Estimate effect size for phase 3 planning
 - Interpretation of time to events is problematic in single arm studies
 - Leads to over optimistic interpretation of effect size
 - Consider randomized phase 2 studies
- Adaptive designs with appropriate statistical adjustments may be feasible
 - Make “go – no go decisions”
 - Futility analysis, resizing may be considered
 - Need to reach agreement with statistical reviewers

Planning Later Phase Studies

- End of phase 2 meeting with FDA
 - Justify dose, regimen for phase 3
 - Preliminary Safety profile established
 - Target population
 - Specific proposed indication
 - Assays required for eligibility
 - Prior therapy
 - Proposed control arm
 - Statistical considerations
 - Assessments
 - Preliminary evidence of activity/effect size
- Consider Special Protocol Assessment
 - Agreement regarding the interpretability of study results

Endpoints for approval of Cancer Therapeutics

- Time to Event
 - Survival still the preferred endpoint
 - Unequivocal clinical benefit
 - Progression – needs to be carefully measured
 - PFS preferred over TTP
 - Time to recurrence (in adjuvant indication)

- Radiological Response determination
 - WHO vs. RECIST vs. volumetric measurements
 - Durability determination essential
 - PET/CT - regulatory application less clear
 - Other Biomarkers for response

- Patient Reported Outcomes (should be explored in early phase if intended to support labeling)

See: Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics <http://www.fda.gov/cber/gdlns/clintrialend.pdf>

Endpoint issues specific to Cancer Vaccine Development

- Survival – may be confounded by subsequent therapy, crossover
- Progression – benefit may be delayed due to delayed onset of immune responses
 - Need to consider if vaccine therapy may be continued following progression event
 - Statistical considerations for delayed effects
- Recurrence
 - Logical endpoint for cancer vaccines
- Response Rates
 - Interpretable in single arm studies but problematic from regulatory perspective

Legal Standard for Effectiveness

- Biological Therapeutics are licensed based on “Substantial Evidence” of effectiveness as per the PHS act
- Drugs – FD&C Act and FDAMA
 - “Substantial Evidence”
- Biologics – Section 351 of PHS Act
 - Safety Purity & Potency
 - Potency = Effectiveness (21CFR 601.25)
- Effectiveness is established by “Adequate and Well-Controlled Trial(s)”
 - Accelerated Approval is not “approval lite”
 - R. Pazdur, FDA CDER

H. Fine Editorial JCO 2004

- ...it is important to generate more correlative laboratory data supporting the biologic rationale behind the vaccine strategy and more clinical efficacy data, such as consistent radiographic evidence of an antitumor response, before subjecting a large number of patients to a treatment arm that may be inferior to the new standard of care.

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- CBER Web page <http://www.fda.gov/cber>

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